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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/185,908	11/03/1998	OREST W. BLASCHUK	100086.409.	1195

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EXAMINER	
DECLOUX, AMY M	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/185,908	Blaschuck et al
Examiner	**Art Unit**
DeCloux, Amy	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *11/30/01 and 8/29/01*

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-20, 27-43, 46-49, 52-55, and 58-61* is/are pending in the applica

4a) Of the above, claim(s) *7-20, 33, 34, 38-43, 46-49, 52-55, and 58-61* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-6, 27-32, 35-37,* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5 and 2(*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. The request filed on 8-24-01 (Paper No. 18) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/185,908 is acceptable and a CPA has been established. An action on the CPA follows. It is noted that after-final amendment filed 6-4-01 (Paper No.15) has not been entered as indicated in the advisory action mailed 7-2-01 (Paper No. 16), nor did applicant request that said amendment be entered in their request for a CPA filed 8-24-01 (Paper No. 18).

Applicant's amendment, filed 8-24-01 (Paper No.19), is acknowledged and has been entered. Claims 2-20, 27-43, 46-49, 52-55, and 58-61 are pending. Claims 7-20, 33-34, 38-43, 46-49, 52-55 and 58-61 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Applicant's election WITH traverse of Group I (Claims 2-6, 27-32 and 35-37) in Paper No. 24 filed 11-30-01, is acknowledged. Applicants further elect the following species: five as the specific number of consecutive amino acid residues of CAR sequences, a peptide of 8 amino acid residues and SEQ ID NO:34.

Applicant's traversal is on the grounds that the restriction requirement for the CPA appears to treat the CPA as the application originally filed because certain claims canceled in response to the first restriction requirement (ie claims 21-26, 44-45, 50-51, 56-57 and 62-63) are still regarding as pending in the second restriction. However it is noted by the examiner that said claims were requested to be canceled by applicant in the response to a restriction requirement in the parent, and was not noted by either the examiner or the docket staff. The premise for the current restriction requirement is to bring it in line with the restriction requirements of co-pending applications comprising similar subject matter by the same inventors, and also because of the literally hundreds of peptide species recited in the instant claims, each with a distinct structure and accompanying characteristics.

Additionally, it is noted that a restriction can be applied at any stage of prosecution. However, upon further consideration, the species requirement has been withdrawn.

Because the products of each group are patentably distinct for the reasons of record and because a search in the non-patent literature of any of these distinct inventions would not be co-extensive with a search of the others, and would constitute a serious undue burden on the Examiner, restriction for examination purposes as indicated is proper. The restriction is still deemed proper and is therefore made FINAL.

The AG reference WO 95/06122 in the information disclosure statement filed 8-24-01 has not been considered because it is not in English.

2. With regard to the 102(b) rejection.

Applicants correctly state that claims 1-3, 5-7 and 35 were rejected under 102 b as allegedly being anticipated by Ruoslahti et al (U.S. Patent No. 5,627,263, 1997) in the office action dated 6-30-2000. The examiner notes that said rejection was withdrawn in the final rejection, due to applicant's amendment of claims.

The applicants now incorrectly contend that said reference was incorrectly cited in the advisory action dated 7-2-2001, which was not entered. This is the exact paragraph in said advisory action:

"As reiterated in the previous office action mailed 3/27/01 (Paper No. 15), the 102(b) rejection anticipated by Ruoslahti et al (U.S. Patent No. 5,627,263) has been withdrawn. Applicants point out that the sequence CRGDSFVGC is not taught by said patent and the examiner agrees. Said sequence is actually taught by Ruoslahti et al in U.S. Patent No. 5,981,478 (Table No.3) which if applied would be a 102(e) rejection.".

The examiner notes there is nothing incorrect about said paragraph, and the examiner was just letting applicant know about **potential** rejections.

The applicant further states that the advisory action states that the above claims now stand rejected on under 102 (e) as being anticipated by another US Patent to Ruoslahti et al (U.S.Patent No. 5,981,478). This is incorrect and the examiner points out that the advisory action states " which **if** applied **would be** a 102(e) rejection.".

The applicant further contends that the Advisory action states that Ruoslahti et al teach the sequence of CRGDFVGC. This is incorrect and the examiner points out that the advisory action states "the sequence **CRGDSFVGC** is ....actually taught by Ruoslahti et al in U.S. Patent No. 5,981,478 (Table No.3)".

The examiner agrees with applicant that neither Ruoslahti patent applies to the claims presently recited.

3. The following is a quotation of the appropriate paragraphs of *35 U.S.C. § 102* that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 2 and 5 are rejected under 35 U.S.C. 102(b) as anticipated by Bult et al. (Science 273:1058-1073, 1996) as evidenced by Kohara (1995) genebank submission.

Bult et al teach a 47mer protein that comprises the sequence IYSYX (see entire article) comprising at least 5 consecutive amino acids of SEQ ID NO:1, based on nucleotide sequence of the procaryotic organism Methanococccus jannaschii. Therefore, the referenced teachings anticipate the claimed invention.

5. Applicant traverses the Bult 102 rejection because it teaches the entire genomic sequence of the procaryotic organism Methanococccus jannaschii and applicant contends that it depicts many predicted open reading frames and there is no indication that the sequence is correct or that it is actually a functional open reading frame. It is the examiner's position that there is no reason to doubt the correctness of the sequence given that Bult et al teach that the referenced protein is encoded by said organism. The examiner has also pointed out that said sequence is transcribed in at least another eukaryotic organism as evidenced by the Genbank submission of a mRNA sequence of an eukaryotic organism Caenorhabditis elegans by Kohara (1995) which teaches the cDNA of the mRNA of the gene encoding a protein comprising the sequence IYSY, which does not lead credence to applicant's position that the referenced genomic sequence is not correct and nor that it does not function in an open reading frame. Applicant further contends that said submission indicates it may be translated into one or more of the six possible reading frames. The examiner contends that there are only three reading frames and that it does not indicate which reading frame is translated. However it is the examiner's position given only three reading frames, that the open reading frame is inherent to the referenced RNA, and the open reading frame to be considered is that which would produce the claimed protein. Since the Office is not equipped to manufacture the claimed protein and/or the protein coded by the referenced nucleotides, nor to conduct comparisons, the burden is on the applicant to establish a patentable distinction between the claimed and referenced proteins. See In re Best, 195 USPQ 430, 433 (CCPA 1977).

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2-6, 27-32 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 2-6, 27-32 and 35-37 are drawn to a cell adhesion modulating agent that comprises a claudin CAR sequence and contains as few as 3 amino acids and as many 50 amino acid residues. However, the specification does not enable one of skill in the art regarding how to make and use the agent. Applicant has generated this deduced consensus amino acid sequence for a claudin CAR sequence (SEQ ID NO:1), based on a sequence homology alignment of the amino acid sequences of extracellular

domain one of representative mammalian claudins as indicated in Figure 1 of the instant specification. Applicants have disclosed that an agent comprising said claudin CAR sequence is capable of modulating claudin-mediated processes, such as cell adhesion, (see page 14, lines 10-21 of the instant specification). However, there is no clear guidance from Applicant's specification that an agent comprising SEQ ID NO:1 is capable of modulating claudin-mediated processes, such as cell adhesion, because applicant has not disclosed the sequence identity of CAR containing peptides that actually reduce cell adhesion in the disclosed example, nor the 9 amino acid CAR sequence used to make the antibodies that have cell adhesion modulating activity as disclosed in Examples 2 and 4. The only proposed uses for the an agent comprising the claimed CAR sequence are based upon an alignment with other mammalian claudins, and there is no predictability that this small sequence identity (or which part(s) thereof) would confer the biological activities including modulating claudin-mediated processes, such as cell adhesion, to an agent comprising the claimed CAR sequence (SEQ ID NO:1) because Applicant has not disclosed where the biological activity of cell adhesion of the claudin resides within the (SEQ ID NO:1 .

Furthermore, there is no clear guidance from Applicant's specification of the minimum number of amino acids from the deduced consensus amino acid sequence for a claudin CAR sequence (SEQ ID NO:1) is necessary to modulate claudin-mediated processes, such as cell adhesion. For example, claims 5 and 6 recite an agent of a peptide from 5-50 and 5-16 amino acid residues, respectively. Applicants disclose the deduced consensus amino acid sequence for a claudin CAR as having the sequence of SEQ ID NO:1 which contains 8 amino acids, and of those 8 amino acids, three can be any amino acid. However, there is no clear guidance from Applicant's specification that an agent containing a three amino acid sequence where only the first amino acid is defined as being an Arg or a Lysine, as defined by SEQ ID NO:1, is capable of modulating claudin-mediated processes, such as cell adhesion. Similarly claims 2 and 3 recite a minimum of 5 or 7 consecutive amino acid residues SEQ ID NO:1, and there is no clear guidance from Applicant's specification that an agent of only 5 or 7 amino acids is capable of modulating claudin-mediated processes, such as cell adhesion. Based upon the paucity of information contained within the instant specification in this regard, and within the art at the time the invention was made, it would require an undue amount of experimentation on the part of one skilled in the art to use the claimed polypeptide for the asserted utilities. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Furthermore, there is no clear guidance from Applicant's specification what the effect of cyclization of a claudin CAR sequence will have on it cell adhesion functions. It is known in the art that even single amino acid in a protein's amino acid sequence can have dramatic effects on the protein's function. Since the amino acid sequence of a polypeptide determines its structural, immunogenic and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires detailed knowledge of the ways in which a polypeptide's structure relates to its function. In view of the insufficient guidance in the prior art and in applicants disclosure of the effect of cyclization of a claudin CAR sequence on its functions including cell adherence, making and using the claimed agent is complex and well outside the realm of routine experimentation.

In view of the quantity of experimentation necessary to use the claimed invention, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute.

8. Applicants traverse said rejection on the grounds that the reasonable basis that the specification lacks enablement has not been established because no evidentiary skill is provided to indicate that one of ordinary skill in the art would doubt the cell adhesion modulating agents of the claimed invention. It is the examiner's position that the instant specification is not enabling because an enabling specification must contain a teaching of the manner and process of using the invention in terms which correspond to the scope to those used in defining and describing the subject matter sought to be patented. The examiner notes that applicant has not disclosed the sequence identity of the so called representative modulating agents on NRK cell adhesion disclosed in Examples 2 and 4. Given the insufficient guidance and direction in the instant disclosure regarding the efficacy of the claimed peptide in modulating cell adhesion and given the prior art only teaches that the entire claudin-1 protein is involved in cell adhesion, one of ordinary skill in the art could not predict which if any peptides encompassed by the instant claims would actually reduce cell adhesion, and thus function as a cell adhesion modulating agent.

The unpredictability faced by one of ordinary skill in the art is evidenced by the disclosed generation of a deduced consensus amino acid sequence for a claudin CAR sequence (SEQ ID NO:1), based on a sequence homology alignment of the amino acid sequences of extracellular domain one of representative mammalian claudins as indicated in Figure 1 of the instant specification, without a corresponding correlation of said sequence

to function. Applicant contends that one of ordinary skill in the art would appreciate that the portion of a protein important for, or essential to, the function of the protein is usually highly conserved throughout evolution. However, the examiner notes the word "usually" and notes that there is insufficient guidance from Applicant's specification that an agent comprising SEQ ID NO:1 wherein said agent comprises no more than 50 consecutive amino acid residues present within the claudin (of the 200+ residues found in the full length claudin protein) is capable of modulating claudin-mediated processes, such as cell adhesion, and also notes the lack of disclosure of the 9 amino acid CAR sequence used to make the antibodies that have cell adhesion modulating activity as disclosed in Examples 2 and 4. Therefore, without further guidance from the specification, one of ordinary skill in the art would not be able to predict that this small sequence identity (or which part(s) thereof) would confer the biological activities including modulating claudin-mediated processes, such as cell adhesion, to an agent comprising the claimed CAR sequence (SEQ ID NO:1) because Applicant has not disclosed where the biological activity of cell adhesion of the claudin resides within the (SEQ ID NO:1) and if this consensus sequence alone is sufficient.

Applicant further states that an example attached to the amendment filed 8-24-01, as well as two figures in a related application indicate that a peptide comprising SEQ ID NO:1 is capable of inhibiting the formation of tight junctions in epithelial cells. With respect to the other secondary considerations, the arguments of counsel cannot take the place of objective evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). When any claim of any claim of an application is rejected to or objected to, any evidence submitted to traverse the rejection or objection on a basis not otherwise provided for must be by way of an oath or declaration under 37 CFR 1.132, (see MPEP 716). Applicant may consider entering the above mentioned material in a 1.132 declaration.

Therefore, though applicant's arguments have been carefully considered, they are not deemed persuasive, and said rejection is maintained.

9. Claims 2-6, 27-32 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a cell adhesion modulating agent , comprising a claudin CAR sequence, which comprises at least 5, 7 or 8 consecutive amino acid residues of a claudin CAR sequence having the formula of SEQ ID NO:1. It is noted that SEQ ID NO:1 is an 8mer in which 3 residues can with one exception be any amino acid. A claudin CAR sequence is disclosed as comprising a consensus

sequence of 8 amino acids (SEQ ID NO:1), of which three amino acids are "independently selected". However, it is not clear from the disclosure, exactly which amino acids can be included in the group of "independently selected" amino acids and still comprise a claudin CAR sequence. It is not clear from the disclosure whether the independently selected amino acids must be present in an equivalent position as one of the sequences used to derive the claudin CAR consensus, or if other sequences may be substituted. Since only a consensus sequence of ambiguous length and sequence composition is disclosed, a claudin CAR sequence is not adequately described. Applicant has not adequately described what sets apart claudin sequences as a genus from sequences which are not claudin sequences.

10. Applicant traverses said rejection on the grounds that in view of the description in the instant specification one of ordinary skill in the art would be able to distinguish claudin sequences from those that are not, and that the specification defines claudin as an integral membrane protein with a molecular weight of approximately 22KD and which displays at least 30% sequence identity to a member of a claudin family specifically recited in the present application. However it is the examiner's position that this definition defines claudin, but not a claudin CAR. Therefore, though applicant's arguments have been carefully considered they are not deemed persuasive, and the rejection is maintained.

11. claims 2-6, 27-32 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are not supported by the specification or by the claims as originally filed. There is no support in the specification or claims as originally filed for the recitation "wherein Aaa is not glycine when Lys/Arg is Arginine and Baa is aspartic acid". There is no written description of the claimed invention in the specification or claims as originally filed. Thus the claimed invention constitutes **new matter,** by virtue of introducing a negative limitation, see Ex parte Grasselli 231 USPQ 393.

12. Applicant traverses the rejection on the grounds that the modulating agents described in the instant specification on page 4, line 15 to page 10, line 10, and page 14, line 24 to page 38, line 18, inherently include agents "wherein Aaa is not glycine when Lys/Arg is Arginine and Baa is aspartic acid", and thus are sufficiently supported. While the indicated pages may include numerous examples of sequences which would fall within the scope of SEQ ID NO:1 having the negative limitations recited in the "wherein" clause of claims 2-4, these various examples cannot support the recitation of the

new subgenus of sequences of SEQ ID NO:1 having the negative limitations. Applicant has nowhere pointed out that these examples were members of a particular subgenus to be distinguished from other members of the broader invvention. Therefore, the claimed invention constitutes **new matter,** by virtue of introducing a negative limitation, see Ex parte Grasselli 231 USPQ 393. Applicants cite the Johnson case, however said case does not fit the instant fact situation. In the Johnson case, the grandparent application contained a broad and complete generic disclosure, coupled with extensive examples fully supportive of the limited genus later claimed. In contrast, the instant application contains only two examples of species (peptides with RVT or RVS) within the subgenus presently claimed.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. a message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Amy DeCloux, Ph.D.
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February 8, 2002

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ART UNIT ~~182~~ 1644